

Pacing-Induced Cardiomyopathy

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KEYWORDS

• Pacing-induced cardiomyopathy • Pacemaker • High-burden right ventricular pacing

KEY POINTS

- Pacing-induced cardiomyopathy (PICM) is a well described phenomenon that occurs in a minority of patients exposed to high-burden right ventricular (RV) pacing.
- Although several risk factors may identify patients at increased risk of PICM, many individuals tolerate high-burden RV pacing for many years without obviously deleterious effects, and the ability to identify those at highest risk remains insufficient.
- Treatment of PICM has primarily involved upgrade to cardiac resynchronization therapy once signs of cardiomyopathy manifest.
- The emergence of His bundle pacing may offer an opportunity to prevent PICM before it occurs.

Over 1,000,000 pacemakers are implanted annually worldwide, with approximately half for a diagnosis of high-degree atrioventricular (AV) block.¹ Although many individuals tolerate high-burden right ventricle (RV) pacing for many years without clinically discernible adverse effects,² it has been increasingly recognized that chronic RV pacing may lead to compromised left ventricle (LV) function and may result in symptoms of heart failure (HF), a syndrome known as pacing-induced cardiomyopathy (PICM). Although the exact incidence of PICM and the risk factors that lead to its development continue to be defined, given the large number of pacemakers implanted and the significant percentage of patients with high-burden RV pacing, the potential public health and economic impacts of PICM are substantial, and strategies to prevent and treat it are of clinical importance.

INCIDENCE AND DEFINITIONS OF PACING-INDUCED CARDIOMYOPATHY

The reported incidence of PICM has varied based on different definitions used to identify the

syndrome. The most commonly utilized definitions invoke a drop in LV ejection fraction (LVEF) in the setting of high-burden RV pacing. In a study of 257 patients with normal baseline LVEF, the incidence of PICM (defined as a drop in LVEF $\geq 10\%$ and resulting in an LVEF $< 50\%$) was 19.5% at a mean follow-up of 3.3 years.³ In a similar study, using a definition of drop in LVEF of greater than 5% from baseline in conjunction with symptoms of HF, in a cohort of 234 patients, Lee and colleagues⁴ reported an incidence of PICM of 20.5% at a mean follow-up of 15.6 years. Using a broader definition of PICM to include both drop in LVEF (to $\leq 40\%$) or need for upgrade to cardiac resynchronization therapy (CRT), in a cohort of 823 patients with normal baseline LVEF ($> 50\%$) undergoing permanent pacemaker (PPM) implantation for complete heart block (CHB), Kiehl and colleagues⁵ reported an incidence of PICM of 12.3% at a mean follow-up of 4.3 years. Among randomized, prospective data in the Pacing to Avoid Cardiac Enlargement (PACE) study, 177 patients with normal baseline LVEF were randomized to CRT pacing or RV pacing.⁶ Although the

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inclusion criteria for the PACE study required LVEF greater than 45% at baseline, the mean LVEF of patients enrolled in the study was 61.7%. At 12 months, mean LVEF dropped to 54.8% in the RV pacing group, but remained stable at 62.2% in the CRT pacing cohort ($P < .001$). The decrement in LVEF in the RV pacing arm was also associated with a significant increase in LV systolic volume. During longer-term follow-up from the same study (mean 4.8 years), the groups continued to diverge, with further decrement in LVEF in the RV pacing group to a mean of 53.2% and continued increase in LV systolic volumes, whereas those parameters were stable in the CRT pacing arm.⁷ Additionally, despite the relatively modest drop in LVEF in the RV pacing arm, the incidence of HF hospitalization in PACE was significantly greater in the RV pacing group (23.9 vs 14.6%, $P = .006$).

Although assessment of LVEF has featured prominently in many studies reporting the incidence of PICM, the development of HF symptoms or incidence of HF hospitalization also contributes importantly to the definition of the syndrome. In the MDe Selection Trial (MOST), comparing single-chamber ventricular pacing to dual-chamber pacing in sinus node dysfunction, in analyses adjusted for baseline covariates, the incidence of HF hospitalization was nearly 2.5 fold higher in the dual-chamber pacing arm among those with greater than 40% RV pacing burden compared with those with lower burdens of ventricular pacing.⁸ In contrast to predominantly sinus node dysfunction in the MOST study, in a claims database of over 21,000 patients undergoing pacemaker implantation, the risk of a new HF diagnosis after device implant was significantly higher among those with a diagnosis of AV block (used as a surrogate for increased RV pacing burden), compared with those without a diagnosis of AV block (adjusted hazard ratio [HR] 1.62, 95% confidence interval [CI] 1.48 - 1.79).⁹ Interestingly, in this analysis, the hazard associated with high-burden RV pacing was most notable within the first 6 months following pacemaker implantation, suggesting a more acute risk of HF symptoms than has been appreciated previously. Similarly, among patients with predominantly AV nodal disease in the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (Block HF) study, the clinical composite score incorporating New York Heart Association (NYHA) class, HF hospitalization, and subjective assessment of HF symptoms and quality of life was significantly better in the CRT arm than among those randomized to RV only pacing.¹⁰ Importantly, patients enrolled in Block HF already had some degree of LV dysfunction at baseline (LVEF <50%), and the results suggest that the hazard associated with high-burden RV pacing

may be even more notable among those with baseline impairment of LV function. In a cohort of patients with impaired LVEF who were candidates for defibrillator implantation, the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial demonstrated that the cumulative incidence of death or HF hospitalization was over 30% at 18 months among those with greater than 40% RV pacing, compared with an incidence of less than 10% in the group with less than 40% RV pacing.¹¹ In a similar cohort of patients eligible for defibrillator implantation, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II demonstrated that at 3-year follow-up, RV pacing burden greater than 50% was associated with a nearly twofold increased risk of new or worsened HF, based on investigator-assessed symptoms or need for augmentation of pharmacologic therapy.¹²

In aggregate, these data suggest that approximately 10% to 20% of individuals with baseline normal LV function will develop a significant drop in LVEF within the first 3 to 4 years following high-burden RV pacing. For many of these patients, RV pacing also leads to the development of clinical HF symptoms and significantly increases the incidence of HF hospitalization. The risks associated with PICM may be even more notable among those with baseline impairments in LV function. Although a significant body of literature supports the existence of PICM as a distinct clinical syndrome, it appears likely that not all patients are equally susceptible to the detrimental effects of high-burden RV pacing. Among a cohort of 286 patients undergoing AV junction ablation resulting in obligate high-burden RV pacing, no significant decrement in LVEF was noted at a mean follow-up of 20 months, and the 10-year incidence of HF hospitalization in this cohort was only 8%.² In a similar single-center study from Germany, among 791 patients with baseline normal LVEF (>55%), during a mean follow-up of 44.2 months, only 5% of patients developed a drop in LVEF to no more than 40%, and the burden of RV pacing was not a significant multivariate predictor of LV function decrement,¹³ possibly suggesting a more complex interplay of risk factors. These studies demonstrate that much remains to be learned about risk factors for the development of PICM, as discussed in the following sections.

In addition to deterioration of LV function and HF events, it has been suggested that the development of atrial fibrillation (AF) may also be a manifestation of PICM in certain patients. In a randomized trial of atrial versus dual-chamber pacing for sinus node dysfunction in 177 patients, higher burden ventricular pacing in the dual-chamber arm was associated with a significantly

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